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EXAMINER	
MEAH, MOHAMMAD Y	
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1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/650,592	AFEYAN ET AL.	
	Examiner	Art Unit	
	MD. YOUNUS MEAH	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *56,110,135,137,147 and 150* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *See Continuation Sheet* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 5,7-9,26,27,29,31,37,48-51,56,58,69,70,72,74,76,78,108,110,117,127-129,131-135,137,147,150,156 and 157.

Continuation of Disposition of Claims: Claims rejected are 5,7-9,26,27,29,31,37,48-51,58,69,70,72,74,76,78,108,117,127-129,131-134,156 and 157.

DETAILED ACTIONnnn

Claims 5, 7-9, 26-27, 29, 31, 37, 48-51, 56, 58, 69-70, 72, 74, 76, 78, 108, 110, 117, 127-129, 131-135, 137, 147, 150 and 156-157 are pending. With supplemental amendment of this application filed 11/4/08, the applicants' amended claim 5, and canceled claim 35. Claims 56, 110, 135, 137, 147 and 150 remain withdrawn.

Claim Rejections

35 U.S.C 112

35 USC 112 2nd paragraph

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 69 and 74 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 69: The recitation of the term "resistant to cleavage by the protease domain" renders the claim indefinite because the resulting claim does not set forth the metes and bound of the desired patent protection. The phrase is a relative term. The specification does not define the phrase and one of ordinary skill in the art would be able to determine the boundary of the claim. For the examination purpose only, the phrase is ignored because no reasonable interpretation could be made.

Claim 74, the recitation of the term "reduces a biological activity" makes the claim unclear because "reduces a biological activity" is a relative term. For examination purpose only, the phrase is assumed to mean that the adzyme reduces the effects of the substrate in a biological system relative to untreated biological system.

35 U.S.C. 112 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5, and its dependent claims 7-9, 26-27, 29, 31, 37, 48-51, 56, 58, 69-70, 72, 74, 76, 78, 108, 110, 117, 127-129, 131-135, 137, 147, 150,156-157 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. These claims are directed to a genus of adzymes comprising fusion enzymes optionally through a linker polypeptide with a genus of antibodies, proteins, peptides which provide a targeting moiety, wherein said targeting moiety is engineered by any means. The specification teaches fusion proteins constructed by gene fusion of known protein with binding ability to a substrate, such as adzyme comprising trypsinogen fused to sp55, an antibody (page157). However, specification does not teach fusion protein, wherein the polypeptide comprising binding domain designed by protein engineering on a template or *de novo* protein design in order to get desired binding activity to a substrate. The term "engineered protein" can mean any thing from a single substitution mutation to *de novo* design of protein with desired binding properties. Although there are limited successes in the prior art in introducing some desired properties or functionality into a protein, the methodology remains limited

to particular example and there are no general rules or methodology for engineering proteins to produce a polypeptide with desire binding capabilities. The specification fails to teach a general method of designing or engineering proteins with desired activities such as binding a target peptide or polypeptide. Given this lack of description of teaching a general method for designing proteins or representative species of designed binding proteins to substrates encompassed by the claims, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Claims 5 and its dependent claims 7-9, 26-27, 29, 31, 37, 48-51, 56, 58, 69-70, 72, 74, 76, 78, 108, 110, 117, 127-129, 131-135, 137, 147, 150,156-157 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an adzyme comprising a protease catalytic domain fused to a well define protein capable of binding a target substrate such as an antibody, does not reasonably provide enablement for adzyme formed by the fusion of a catalytic domain and a binding domain engineered by any means. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

According to MPEP 2164.01(a), factors considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy

the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

MPEP§ 2164.04 states that while the analysis and conclusion of a lack of enablement are based on the factors discussed in MPEP § 2164.01(a) and the evidence as a whole, it is not necessary to discuss each factor in the written enablement rejection. The language should focus on those factors, reasons, and evidence that lead the examiner to conclude that the specification fails to teach how to make and use the claimed invention without undue experimentation, or that the scope of any enablement provided to one skilled in the art is not commensurate with the scope of protection sought by the claims. Accordingly, the factors most relevant to the instant rejection are addressed in detail below.

The breadth of the claims: Claims 5 and its dependent claims 7-9, 26-27, 29, 31, 37, 48-51, 56, 58, 69-70, 72, 74, 76, 78, 108, 110, 117, 127-129, 131-135, 137, 147, 150,156-157 encompass adzyme comprising a fusion protein comprising of a catalytic domain and a binding domain engineered by any means.

The state of the prior art, the relative skill of those in the art, and the predictability or unpredictability of the art: The specification teaches recombinant proteins, such as adzyme comprising trypsinogen fused to sp55, an antibody (Page 157). However, the

specification does not teach a fusion protein, wherein the polypeptide comprising binding domain engineered by any means, i.e., made by any substitution, deletion, and insertion mutation, multiple mutations, of polypeptide of known binding domain (sp55, an antibody) or a *de novo* designed protein that is capable of binding a desired substrate. Reconstructing a binding protein or *de novo* design a protein to bind to a specific binding target substrate is neither known nor routine in the art. The use of molecular modeling and three-dimensional structures of known protein may produce some desirable effect on limited scale involving changes of no more than handful of amino acid residues. See at least the abstract of Skerra J. Mol. Recogn. 2000, 13, 167-187. The specification does not teach any methodology for redesigning or *de novo design* protein capable of binding any target protein, and the prior art does not provide well know reliable methodology for designing proteins that bind to a target protein with high affinity and specificity that would be required for the claimed invention. Skerra teaches that the *de novo* design of protein usually does not result biologically active protein molecule because of proper folding of the engineered protein to adapt structurally well-defined polypeptides having novel function (Page 167 right column last paragraph and page 168 left column 1st paragraph).

The amount of direction provided by the applicants; and the existence of working examples: The specification teach recombinant fusion proteins, such as adzyme comprising trypsinogen fused to sp55, an antibody sp55 (Page 157). The specification does not teach any polypeptide binding domains that is engineered on a template to bind a specific substrate or *de novo* designed to bind a specific substrate. The

specification fails to describe a general method for designing any binding site to any substrate.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims including an adzyme, wherein the binding domain polypeptide engineered by any means. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of substances having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

35 U.S.C 102

Rejection of Claims 5 and 7-9, 26, 27, 31, 37, 69-70, 72, 74, 78, 108, 117, 127-129, 156 and 157 under 35 U.S.C. 102(b) as being anticipated by Davis *et al*. (WO 00/64485) is withdrawn after applicants amendment of claim 5.

Claims 5, 7-9, 37, 48-51, 58, 69-70,72, 74, 76, 78,108,127-129, 156 and 157 are rejected under 35 U.S.C. 102(b) as being anticipated by Holvoet *et al*. (JBC 1991, vol.266, pp 19717-19724).

Holvoet *et al*. teach (page 19717 paragraph 1 and 2) fusion proteins of Urokinase – a serine protease-fused with a fibrin-specific antibody (variable region Fv) molecule. The resulting fusion protein shows 13-fold increase of the fibrinolytic potency. This

fusion protein targets a blood clot in blood vessel, human plasma (Fig. 7, page 19722, anticipate claims 5, 7-9, 37; blood clots are component of atherosclerotic plaque, claim 48 and 108) wherein antibody domain binds on fibrin and protease domain lyses the clot (page 19723, column 2 parg 2-4). Holvoet *et al.* teach the purification of their fusion protein using a Kalikrein inhibitor (page 19719 left column 4th parg; anticipates claim 58). The blood clot binds antibody in-vivo; and fusion protein alters its binding specificity and biological activity (claims 70, 74, 76, 78) and said blood clot is endogenous to human patent (substrate, claim 7). Since Holvoet et al. fusion protein comprising protease-fused with a fibrin-specific antibody (antibody is a polypeptide molecule, anticipate claim 156) is stable enough to lyse blood clot; it is resistant to autocleavage (claim 69, 129, 157). Since Holvoet *et al.* fusion protein shows 13-fold increase of the fibrinolytic potency, targets a blood clot and lyses blood clot; it can be used as pharmaceutical composition for the treatment of blood clot or heart disease (claims 127-129) in human. Claims 48-51 are included in rejection because the prior art meets all the structure limitation of the claimed invention and the additional limitations in claims 48-51 appears to be intended use of the claimed invention. Intended use limitations do not carry a patentable weight.

CLAIM Rejection - 35 U.S.C 103a

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a)A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 117 is rejected under 35 U.S.C. 103(a) by Holvoet *et al.* (JBC1991, vol.266, pp 19717-19724) or Bhatia *et al.* (Intl. J. Cancer 2000, 85, 571-577) in view of Davis *et al.* (WO 00/64485).

Holvoet *et al.* are summarized above. Holvoet *et al.* does not teach said fusion proteins comprise chymotrypsin or matrix metalloproteinase as protease.

Davis et al. teach fusion proteins made by conjugating enzymes such as chymotrypsin or matrix metalloproteinase with targeting domain comprising ligand or substrate binding domain or protein or peptide or antibody via a linker wherein the protease catalyzes the cleavage of peptide bond of a substrate polypeptide of blood stain. However Davis et al made the fusion protein by chemical conjugation, not by gene fusion technique.

Bhatia *et al.* teach that production of chimeric protein by gene fusion technique have advantages over chemical conjugation, such as, tailored proteins can be made, easier to make larger quantities (page 771 column 1 3rd parg).

Therefore, one of ordinary skill in the art is motivated to make the protein conjugate of Davis *et al.* comprising chymotrypsin conjugated to antibody by gene fusion methodology as taught by Holvoet et al or Bhatia et al. and use it to cleave the substrate of polypeptide of blood stain.

As such it would have been obvious to one of ordinary skill in the art to make the fusion protein of Davis et al. by the method Bhatia et al. or Holvoet et al. and use the resulting adzyme to inactivate substrate polypeptides by catalyzing the proteolytic cleavage of the said substrate polypeptide of blood stain.

Claims 26, 27, 29 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Holvoet et al. (JBC1991, vol.266, pp 19717-19724) in view of Guo et al. (Biotech. and Bioeng. 2000, 70, 456-463).

Holvoet et al. is described above. Holvoet *et al.* does not teach use of linker in between the catalytic domain and the binding domain.

Guo et al. teach fusion proteins wherein an enzyme (ASNase) is conjugated to an immunoglobulin or fragment thereof or antibody (scFV) by a linker polypeptide $(Gly_4Ser)_3$. Guo et al also teach the advantage of $(Gly_4Ser)_3$ as linker, such as serine enhance hydrophilicity and glycyl residues provide conformational flexibility (page 457, column 1 2nd parg). Therefore, one knowledgeable in prior art is motivated to make fusion proteins comprising enzymes (serine protease) which catalyze degradation of a specific target conjugating through $(Gly_4Ser)_3$ type linker to a binding partners wherein the binding partner is an antibody (immunoglobulin) by the method Holvoet et al.

As such it would have been obvious to one of ordinary skill in the art to make a fusion protein as taught by Holvoet et al and fuse *via* a linker as taught by Guo *et al.* and use the resulting fusion protein to inactivate substrate polypeptides by catalyzing the proteolytic cleavage of the said substrate polypeptide.

Claim 51 is rejected under 35 U.S.C. 103(a) as being unpatentable over Holvoet *et al.* (JBC1991, vol. 266, pp 19717-19724) in view of Debburman *et al.* (PNAS 1997 94, 13938-13943).

The teaching of Holvoet *et al.* is described above, but they do not teach specific target comprising prion protein molecule for their fusion protein.

Debburman et al. teach prion protein comprise protease labile PrPc and protease resistant, PrPSc. Prion molecule involve in deadly disease when prion molecule turn into protease resistant form (page 13938 column 1 2nd parg). One knowledgeable in prior art is motivated to make fusion proteins as taught by Holvoet *et al.* comprising enzymes (protease,) conjugated to binding partners wherein the binding partner is an antibody specific to prion molecule and use it to catalyze degradation of prion molecule before it turn into resistant form.

As such it would have been obvious to one of ordinary skill in the art to make a fusion protein comprising protease conjugated to prion specific antibody molecule by the method as taught by Holvoet et al and use the resulting adzyme to inactivate prion type substrate polypeptides by catalyzing the proteolytic cleavage of the said substrate prion polypeptide.

Claims 131-134 are rejected under 35 U.S.C. 103(a) as being unpatentable over Holvoet *et al.* (JBC1991, vol.266, pp 19717-19724) in view of Sanderson et al. (Medic. Res Rev 1999, 19, 179-197).

Holvoet *et al.* (JBC1991, vol.266, pp 19717-19724) described above.

However, Holvoet et al do not teach said pharmaceutical preparation comprising a reversible inhibitor safe to human.

Sanderson *et al.* (Medic. Res Rev 1999, 19, 179-197) teach small molecule non-covalent binding protease inhibitor that use with pharmaceutical composition which are reversible and safe in human (abstract).

Use of protease inhibitors in protein sample is well known in prior art because proteases autocatalysis their own degradation (Sanderson et al). In order to inhibit the protease to degrade pharmaceutical preparation comprising the fusion protein which catalyze degradation of a specific target to a binding partners wherein the binding partner is an antibody (immunoglobulin), one knowledgeable in prior art is motivated to add reversible protease inhibitor that are safe in human as taught by Sanderson *et al*. As such it would have been obvious to one of ordinary skill in the art to make pharmaceutical preparation comprising a fusion protein as taught by Holvoet et al and combine it with reversible protease inhibitor as taught by Sanderson et al. so that said pharmaceutical preparation is safe for human and effective.

Applicants' argue that Davis et al. chimeric protein is chemically cross-linked protein conjugate and Davis et al. especially teach advantage of chemical cross-linking and therefore one will not motivate to use cotranslation gene fusion technique.

Applicants' arguments files on 11/04/08 have been fully considered, but they found unpersuasive. Bhatia et al (Intl. J. Cancer 2000, 85, 571-577, page 571, 3rd paragraph) provide motivation to make fusion protein by gene fusion method as it teaches the advantages of the recombinant fusion protein such as easier to make, one well defined product obtained, and higher purity product compare to chemical conjugation. Thus one of ordinary skill in the art would have been **motivated** at the time of invention to make protein conjugate comprising two protein partners of Davis et al by gene fusion methodology (as taught by Bhatia et al. Applicants' argument against Guo et al, is

considered but is not found persuasive. Guo et al provide motivation to use $(Gly_4Ser)_3$ as linker. Guo et al teach the advantage of $(Gly_4Ser)_3$ as linker, such as serine enhance hydrophilicity and glycyl residues provide conformational flexibility (page 457, column 1 2nd parg). Therefore, one knowledgeable in prior art is **motivated** to combine Davis et al and Whitcomb et al with Gao et al. as Davis et al itself teach to introduce linker group in between catalytic domain and targeting domain and Guo et al, taught how to produce a protein (ASNase) conjugated to immunoglobulin (scFV) by a linker polypeptide $(Gly_4Ser)_3$. One knowledgeable in prior art can make a fusion protein by using chimeric gene comprising mesotrypsin domain, linker group and targeting domain.

Double Patenting Rejection

Provisional rejection of claims 5, 7-9, 26-27, 29, 31, 35, 37, 52-53, 58, 69-70, 72, 74, 76, 78, 108, 119 and 127-29, 131-134, are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 4-5, 30-34 37-41 of copending Applications No.10/792,498 and 10/650,591 is remain.

Examiner agrees with applicant that the provisional obviousness-type double patenting rejections may be withdrawn when all claims are otherwise allowable if the copending application is not allowed (however see MPEP 804 I(B)(1) for situations where this may not be the case) or when applicants submit a terminal disclaimer, however until one of these conditions apply the rejections will be maintained.

Allowable Subject Matter/Conclusion

None of the claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mohammad Meah whose telephone number is 571-272-1261. The examiner can normally be reached on 8:30-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, NASHAAT T NASHED can be reached on 571-272-0934. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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